REMARKS

Claims 6, 7, 20, 24, 27 and 30-32 are active. Claims 8, 9, 21-23, 25, 26, 28 and 29 have been withdrawn from consideration. Claim 20 has been amended as suggested by the Examiner. Claim 24 has been placed in independent form. This claim has been indicated as being allowable if it included the limitations of the claims from which it depended. To address the concern expressed in the Advisory Action, Claim 24 now deletes language (incorporated from independent Claim 6) deemed indefinite and now simply indicates that component (B) is isolated zingerol. Accordingly, the Applicants do not believe that any new matter has been added. Favorable consideration and allowance of this application is now respectfully requested.

Request that the Finality of the Official Action be Withdrawn

The last Official Action was made first-action-FINAL. However, new prior art (e.g., Hiromitsu, JP 363267255A and Suekawa et al.) has been applied and new grounds of rejection added (e.g., under 35 U.S.C. 103 and on obviousness-type double patenting grounds). This is the first notice that Applicants have had regarding this new prior art and these new rejections and they have not yet had an opportunity to respond. Accordingly, the Applicants respectfully request that the finality of the last Official Action be withdrawn.

Election/Restriction

The Applicants previously elected Group II (method of treatment) and the a species of compound for use in the elected method comprising (A) chlorogenic acid and (B) a central nervous system stimulating component. The Restriction Requirement has been made FINAL. On June 2, 2005 the Applicants were required to further elect a single species of component (B) and subsequently elected (B) zingerol which is a heat component of ginger

(*Zingiberaceae*). The claims as directed to the elected species (A) chlorogenic acid + (B) zingerol have been found in condition for allowance except for formal matters. Since zingerol falls within the subgenus of isolated heat component of *Zingiberaceae* described in Claim 6, the Applicants respectfully request that heat components related to zingerol from this subgenus be examined.

Status of Rejections

Based on the remarks in the Advisory Action, the Applicants believe that the amendment of Claim 24 above should address all the rejections, except for the obviousness rejection based on Cheng and Suekawa and certain obviousness-type double patenting rejections. The response to the obviousness rejection appears immediately below and the Applicants prior responses to the other final rejections are reiterated below it.

Rejection—35 U.S.C. § 103

Claims 6, 7, 20 and 27 were rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al., Chinese Pharm. Journal 46:575 and Suekawa et al., Nippon Yakurigaku Zasshi 88:339 (English Abstract). This rejection is premised on two disparate references teaching that either chlorogenic acid alone or capsaicin alone can reduce blood pressure. Neither reference suggests the combination of chlorogenic acid and capsaicin, rather the motivation relied on by the rejection is that each of these substances alone reduces blood pressure and therefore it would have been obvious to one of ordinary skill in the art to combine these substances and expect to get a reduction in blood pressure.

The prior art teaches away from the claimed combination by indicating that the administration of capsaicin actually increases blood pressure. Suekawa indicates that capsaicin 0.1 mg/kg caused a "rapid fall in blood pressure" followed by marked pressor

responses (i.e., marked increases in blood pressure) in rats. While Suekawa indicates that administering capsaicin reduces blood pressure, this reduction is rapid, and is followed by an increase in blood pressure. Thus, based on Suekawa one with ordinary skill in the art would not have administered capsaicin to a patient with hypertension because while providing an immediate reduction in blood pressure it would have eventually increased blood pressure and such an increase would have been detrimental or risky for a patient having hypertension.

Secondly, the cited prior art in combination does not provide a reasonable expectation of success for decreasing blood pressure using the claimed combination. As discussed above, administering capsaicin produces a delayed pressor effect increasing blood pressure, but Cheng indicates that the administration of chlorogenic acid produces delayed effect on reducing blood pressure ("the maximal effect was not observed until at least 50 min after the drug injection", middle of page 578). Thus, one with ordinary skill in the art would not have had a reasonable expectation of success in reducing blood pressure by combining chlorogenic acid and capsaicin, because the cited prior art suggests that this combination would be antagonistic. That is, that the delayed blood pressure reducing effect of chlorogenic acid would have been negated by the delayed blood pressure increasing effect of administering capsaicin. Therefore, one with ordinary skill in the art would have avoided administering capsaicin based on the disclosure that it raises blood pressure, and would not have had a reasonable expectation of success that the combination of these two substances to treat hypertension based on the antagonism suggested by the cited art. Accordingly, the Applicants respectfully request that this rejection be withdrawn.

Rejection—35 U.S.C. § 112, second paragraph

Claim 20 was rejected under 35 U.S.C. 112, second paragraph, as indefinite. This rejection is moot in view of the amendment above which defines the degree of hotness of the heat components by reference to heat components exemplified in the specification.

Rejection—35 U.S.C. § 103

Claims 30-32 were rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al., Chinese Pharm. Journal 46:575 in view of Hiromitsu, JP 363267255A (English Abstract). Examination encompasses the previously elected species (zingerol + isolated chlorogenic acid) and the currently elected species (capsaicin + isolated chlorogenic acid). This rejection concerns the previously elected species.

Cheng, Table 1 on page 579, refers to the effects of chlorogenic acid and the Abstract indicates that "chlorogenic acid. . .at higher doses possessed the delay (sic) hypotensive effect". Table 1 shows the effect of chlorogenic acid on arterial blood pressure of spontaneously hypertensive rats. However, Cheng does not disclose zingerol or combination of chlorogenic acid with zingerol.

Hiromitsu was cited as disclosing that "ginger liquid" (not necessarily containing zingerol) is useful "for depressing blood pressure". However, this statement appears anecdotal and there are no examples of the effects of ginger liquid as produced by the method described in the abstract on hypertension. Thus, this document does not provide a reasonable expectation of success for treating hypertension using ginger liquid. Moreover, there is no suggestion in Hiromitsu to combine ginger liquid with isolated chlorogenic acid to treat hypertension.

On the other hand, Example 2 of the specification shows the anti-hypertensive activity of such a combination.

Moreover, one with ordinary skill in the art would not reasonably expect that a complex mixture of ingredients of Hiromitsu and chlorogenic acid would necessarily exhibit any effect on hypertension since the interaction of the Hiromitsu "ginger liquid" composition with chlorogenic acid could negate or inhibit the effects observed by Cheng. Common drug interactions include pharmacodynamic (where one drug competes for the same receptor site as another) and pharmacokinetic (where the absorbtion, distribution, metabolism or excretion of one drug is affected by the presence of another). For example, it is commonly known that consumption of grapefruit juice inhibits the uptake or activity of many drugs (see Oesterheld, previously submitted). Due to complexity of the mixture of Hiromitsu and the possibility of drug interactions which negate the hypertensive effects of chlorogenic acid of Cheng (or alternatively, those of the Hiromitsu composition) one with ordinary skill in the art would not have had a reasonable expectation of success in treating hypertension by merely combining the products of Cheng and Hiromitsu. Accordingly, the Applicants respectfully request that this rejection now be withdrawn.

Rejection—35 U.S.C. § 103

Claim 20 was rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al., Chinese Pharm. Journal 46:575 and Hsia et al., U.S. Patent No. 6,440,464. This rejection is moot in view of the amendment of Claim 20.

Moreover, there is no suggestion in either Cheng or Hsia to combine chlorogenic acid and capsaicin, nor is there any reasonable expectation that this combination of ingredients

would exert a superior antihypertensive effect. As evidenced by Suekawa, which is discussed above, one with ordinary skill in the art would have not had a reasonable expectation of success for combination of these ingredients due to the reported pressor effect exhibited after the administration of capsaicin and the delayed antihypertensive effect of chlorogenic acid administration as disclosed by Cheng. Accordingly, the Applicants respectfully request that this rejection now be withdrawn.

Rejection—Obviousness-type Double Patenting

Claim 20 was rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending U.S. Applications 09/922,694, 10/826,289, 10/632,810, 10/810,611, or 11/106,428, in view of Hsia, U.S. Patent No. 6,440,464.

The cited copending U.S. patent applications were indicated to be directed to methods involving use of chlorogenic acid to treat hypertension. However, no mention is made of the combination of chlorogenic acid and capsaicin.

Hsia et al., U.S. Patent 6,440,464, discloses a complex mixture of ingredients only one of which is capsaicin. While commercially obtained capsaicin is described in col. 4, lines 53-59, there is no suggestion in Hsia for treating hypertension using capsaicin. Thus, there is no suggestion for a method of administering a composition which "consists essentially of chlorogenic acid and capsaicin". In fact, Hsia teaches away from a method using such a composition by disclosing that the novelty of his composition lies in a complex combination of ingredients, see Hsia, col. 3, lines 33-37. Furthermore, the disclosure of Hsia is prophetic even with respect to the complex mixtures disclosed by that patent. While col. 4, lines 1-3, indicates an object of the invention is to provide compositions that will lower blood pressure, there are no examples of the claimed compositions actually reducing blood pressure. Thus,

the Hsia patent merely alleges that the claimed compositions treat cardiovascular disease, but provides no evidence that they do.

Even were there some general motivation to treat hypertension by modifying the methods in the copending claims by incorporating other components, such as capsaicin, Hsia does not disclose the equivalence of capsaicin for this purpose, nor provide a reasonable expectation of success that administering a composition consisting essentially of chlorogenic acid and capsaicin would actually treat hypertension. Hsia does not suggest that the combination of chlorogenic acid and a heat component, such as zingerol or capsaicin, would be effective for treating hypertension. On the other hand, the inventors have discovered this combined effect and it is shown by Example 2 of the specification.

There is no reasonable expectation of success in the prior art for the combined effect, since chlorogenic acid and capsaicin have completely different chemical structures and unlike mixing compounds with similar structures and known functions, these diverse chemical structures provide no reasonable expectation of success for an additive or synergistic effect between them. Thus, with ordinary skill in the art would not reasonably expect that a complex mixture of ingredients of Hsia and chlorogenic acid would necessarily exhibit any reductive effect on hypertension since the interaction of the Hsia composition with chlorogenic acid could antagonize, have no effect, or agonize the effects observed for chlorogenic acid.

Moreover, the Hsia mixture contains components which are known to antagonize the effects of certain drugs. For example, it is commonly known that consumption of grapefruit juice inhibits the uptake or activity of many drugs (see Oesterheld, previously cited) and Hsia, in fact, indicates that grapefruit juice (col. 7, lines 37-43), as well as other complex and potentially suspect juices and herbal components are integral components of his mixture. Furthermore, those with skill in the medical and pharmacological arts recognize the

unpredictability of the effects of administering different types of drugs or biologically active substances at the same time, see the commentary on the adverse effects of administering different drugs together on pages 21-23 of the Principles of Internal Medicine, 16th edition, McGraw Hill, New York (2005)(attached). Commonly known drug interactions include pharmacodynamic (where one drug competes for the same receptor site as another) and pharmacokinetic (where the absorption, distribution, metabolism or excretion of one drug is affected by the presence of another). Moreover, coffee extracts containing chlorogenic acid are known to inhibit the absorption of other drugs, see excerpt from The PDR of Herbal Medicines (attached) and capsaicin is a well-known irritant that increases mucous secretion that could also affect drug adsorption.

Therefore, due to complexity of the mixture of Hsia and the possibility of drug interactions between the Hsia mixture and chlorogenic acid which would negate the hypertensive effects of chlorogenic acid one with ordinary skill in the art would not have had a reasonable expectation of success in treating hypertension by combining chlorogenic acid and the capsaicin ingredient disclosed by Hsia.

Since Hsia does not suggest treating hypertension by administering a composition consisting essentially of chlorogenic acid and capsaicin, nor provide any reasonable expectation of success for using this combination to treat hypertension, the Applicants respectfully request that this provisional rejection now be withdrawn.

Provisional Rejection—Obviousness-type Double Patenting

Claims 6, 7, 20 and 27 were rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending U.S. Applications 09/922,694, 10/826,289, 10/632,810, 10/810,611, or 11/106,428, in view of Suekawa et al., Nippon Yakurigaku Zasshi 88:339.

The Applicants traverse this provisional rejection since Suekawa indicates that capsaicin does not produce a sustained effect in lowering blood pressure, but instead produces an immediate fall followed by a pressor effect which raises blood pressure. Therefore, Suekawa does not provide evidence that addition of capsaicin to the chlorogenic acid based methods in the cited applications would have been an obvious variation. Instead, Suekawa shows the unpredictability of the effects of the administration of capsaicin, since it results in a rise in blood pressure after the initial fall.

Should these provisional rejections be maintained, the Applicants respectfully request that they be held in abeyance pending the identification of otherwise allowable subject matter in the present application, see MPEP 804(I)(B).

CONCLUSION

In view of the above amendments and remarks, the Applicants respectfully submit that this application is now in condition for allowance. Early notification to that effect is earnestly solicited.

Respectfully submitted,

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